The relationship between restless leg syndrome and 25-hydroxy D vitamin in hemodialysis patients

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Abstract

Aim: The purpose is to evaluate the relationship between Restless legs syndrome (RLS) and 25-Hydroxy D [25 (OH) D] vitamin level among hemodialysis patients. Material and Method: Hemodialysis patients, in Cumhuriyet University Faculty of Medicine Department of Nephrology were included in this study. Patients were asked about the diagnosis criteria of the International RLS study group and their laboratory examinations along with 25 (OH) D vitamin levels were assessed. Results: Seventy-five patients, 40 of whom were female, were included in the study. The average age of patients was 57.8 (19-84). Average 25 (OH) vitamin D levels of 75 patients in total were found to be 12.6 ±6.27 (3-30). Five patients had 25 (OH) D vitamin insufficiency and 70 had 25 (OH) D vitamin deficiency. Thirty-three patients were diagnosed with RLS and their average vitamin D levels were 10.76 ±4.56; the D levels of 42 patients not diagnosed with RLS were found to be 14.18±7.02. A significant relationship was determined between the patients diagnosed with RLS and their vitamin D levels (p=0.018). Discussion: A significant relationship was determined between RLS and 25 (OH) vitamin D level among hemodialysis patients. The fact that frequency of RLS was higher among hemodialysis patients compared to the general population may be related to low levels of 25 (OH) D vitamin.

Keywords

Hemodialysis; 25 (OH) D Vitamin; Rest-Less Leg Syndrome

DOI: 10.4328/JCAM.5452 Received: 26.10.2017 Accepted:12.11.2017 Published Online: 12.11.2017 Printed: 01.01.2018 J Clin Anal Med 2018;9(1): 65-8
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Introduction

Restless legs syndrome (RLS) is a condition characterized by an uncomfortable sensation, pain and cramp in legs, involuntary leg movements and related sleep disorders which occur especially during sleep at night [1]. Having increasing and more apparent symptoms during resting at night is typical. RLS is diagnosed through the urge to move extremities along with paresthesia or dysesthesia sensations, increasing symptoms during resting and decreasing symptoms during moving, inability to stand still (walking, shaking, contraction, and rubbing) and aggravating symptoms at night. The frequency of RLS is around 5-15% in the general population [2]. Recently, RLS is commonly seen due to end-stage renal failure. Its prevalence has a wide distribution range of 6.6% and 70% among dialysis patients, and it is significantly higher than the rates seen in the general population [1,3-4].

Vitamin D metabolism disorders are commonly seen in chronic kidney diseases (CKD). Vitamin D synthesis is related to the failure of turning 25 (OH) vitamin D into 1.25 (OH) D vitamin in renal dysfunction. Vitamin D deficiency is commonly seen in CKD. In a study conducted by Bansal et al., 45 hemodialysis patients were included in the study and 88.9% of them (n= 40) were diagnosed with vitamin D deficiency [25 (OH) vitamin D < 20 ng/ml] and 29 patients were diagnosed with severe vitamin D deficiency [25(OH) vitamin D < 10 ng/ml]. Two patients were found to have normal levels whereas 3 patients have vitamin D insufficiency (vitamin D between 20-30 ng/mL). It was reported that 23 of these patients (51%) received vitamin D treatment and their average 25 (OH) vitamin D level was 10.14+-8.7 ng/ml [5].

In conducted studies, CKD is indicated as the secondary reason of RLS. However, its etiology is not exactly known. RLS is more commonly encountered in CKD compared to the general population. The purpose of this study was to reveal the relationship between vitamin D level and RLS on the basis of the fact that vitamin D deficiency is frequent in CKD.

Materials and Method

Seventy-five hemodialysis patients who applied to our outpatient clinic and received hemodialysis treatment in our center between March 2012 and May 2012 were included in the study. Chronic renal failure patients who were older than 18 years of age and were receiving hemodialysis treatment at least for three months were included in the study. Patients diagnosed with a peripheral arterial disease, hemiplegia and mentally retarded patients were excluded from the study. Blood samples of patients were analyzed for their 25 (OH) vitamin D, serum iron, iron binding capacity, ferritin, calcium, phosphorus, parathyroid hormone, and complete blood counts before hemodialysis.

Diagnosis criteria specified by the International RLS study group and shown in Table 1 were used for diagnosing of RLS. Diagnosis of RLS has required all diagnosis criteria to be positive.

Statistical analysis

The data obtained from our study were evaluated by using SPSS 14.0 program. Two independent t tests were used when parametric test assumptions were performed, and Mann Whitney U test and Chi-square test were used when non-parametric test assumptions were performed, and level of significance was accepted as 0.05.

Table 1. International RLS study group's diagnosis criteria

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night

Results

A total of 75 patients were included in the study, the average age of patients was 57.8 (19-84), 40 patients were female whereas 35 were male. The average vitamin D levels of 75 patients in total were 12.6 ±6.27 (3-30) ng/ml. Seventy patients (93.3%) had 25 (OH) D vitamin level deficiency (≤ 20 ng/ml), and 5 patients (6.7%) were diagnosed with 25 (OH) D vitamin insufficiency (20-30 ng/ml). Twenty-three of these patients (30.6%) had vitamin D levels of < 10 ng/ml. Tables 2 and 3 illustrate demographic and laboratory data of patients.

Table 2. Laboratory data of patients

	Number	Mean (min-max)	Standard deviation
Age	75	57.8(19-84)	14.5
Vitamin D (ng/ml)	75	12.6 (3-30)	6.2
Hemoglobin (gr/dl)	75	11.0(7,8-16)	1.5
Hematocrit (%)	75	34.4 (24-50)	5.2
Ferritin (ng/ml)	75	955.6 (41-3351)	571.8
Iron (µg/dl)	75	67.6 (18-170)	29.0
Serum iron binding (µg/dl)	75	220.1 (82-340)	52.0
Calcium (mg/dl)	75	8.6(5,6-10,4)	0.85
Phosphor (mg/dl)	75	4.4(1,5-7,7)	1.3
PTH (pg/ml)	74	355.2(6-2219)	439
Kt/V	75	1,29 (1,08-1,56)	0,096

Table 3. Features of patients

	With RLS (33)	Without RLS (42)	Result
Age	59.6±12.9 years	56.65±15.77 years	P > 0,05
Gender Female Male	24 9	16 26	40 35
Vitamin D (ng/ml)	10.76 ±4.56	14.18±7.02	T=2.41 P=0.018
Hemoglobin (gr/dl)	10.74±1.46	11.32±1.65	T=1.60 p=0.114
Hematocrit (%)	33.28±4.90	35.28±5.32	T=1.67 p=0.099
Ferritin (ng/ml)	1007.75±648.30	914.64±508.10	P=0.773
Iron (µg/dl)	70.96±33.97	65.07±24.55	T=0.87 p=0.338
Serum iron binding capacity (µg/dl)	217.65±46.62	222.04±56.47	T=0.35 p=0.722
Saturation of transfer (%)	34.27±19.90	31.71±17.06	P=0.898
Calcium (mg/dl)	8.59±0.69	8.64±0.97	T=0.24 p= 0.805
Phosphorus (mg/dl)	4.42±1.43	4.54±1.37	T=0.37 p=0.706
Parathormone (pg/ml)	321.18±387.43	38.70±479.54	P=0.328

The average age of individuals with RLS was 59.6±12.9 years, and 24 of them were female. The average age of individuals without RLS was 56.65±15.77 years, and 16 of them were female. No difference was found between groups in terms of age. However, a significant difference was found between genders in terms of RLS. (X^2p=0.005). RLS was detected more frequently in female patients. When vitamin D levels (10.76 ±4.56 ng/ml) of 33 individuals with RLS and vitamin D levels (14.18±7.02 ng/ml) of 42 individuals without RLS were compared, a significant relation was determined between vitamin D levels and individuals with RLS (p=0.018).

Twenty-six of individuals with RLS (78.8%) and 32 of individuals without RLS (76.2%) had anemia. When RLS was examined regarding anemia, no statistical difference was found between the two groups. None of the individuals with RLS had low ferritin levels. Two individuals without RLS had low ferritin levels. When RLS was examined regarding ferritin, iron, serum iron binding capacity, saturation of transfer, calcium, phosphorus and parathormone, Kt/V no significant difference was determined.

Discussion

In our study there was no difference between the two groups in the age distribution. The average age of patients was found to be 57,8 (19-84). Average vitamin D levels of 75 patients in total were 12.6 ±6.27 (3-30). Twenty-three of these patients (30.6%) had very low vitamin D levels [25 (OH) vitamin D < 10 ng/ml]. Ninety three point three percent (93.3%) of patients (70) had 25 (OH) vitamin D level deficiency and 6.7% of patients had (5) 25 (OH) vitamin D insufficiency. None of the patients included in the study had a sufficient level of vitamin D. RLS was defined by Ekbom for the first time in 1994. It is characterized by a sensation of discomfort, pain, and cramps in legs and involuntary leg movements which occur especially during sleep at night [1]. RLS is the apparent sensation of discomfort in lower extremities which increase generally at night when complaints are on the rise, with an urge to move legs and decrease when legs are moved. It may be associated with idiopathic, hereditary (primary RLS) or other clinical conditions, and may have secondary reasons such as iron deficiency, end-stage renal failure, pregnancy, rheumatic diseases, and diabetes mellitus. Also, it may also be encountered in neurological conditions (Parkinson, spinal cord lesions, multiple sclerosis, polyneuropathy) [6].

RLS was defined by Callghan for the first time in 20 chronic renal failure patients [7]. In a study conducted by Rogers et al., in 1991, the frequency of RLS was 40% in 55 patients (34 hemodialyses and 21 peritoneal dialyzes) [8]. In a study conducted by Çölbay et al., in Turkey, the frequency of RLS in hemodialysis patients was 43.3% [9].

The fact that RLS symptoms responded to dopamine agonists and levodopa has been considered as proof that dopaminergic dysfunction plays a role in RLS pathophysiology [10]. Additionally, metoclopramide which is a dopamine antagonist showed that pimozide increased RLS symptoms [11-12]. It is remarkable that RLS symptoms increase at night when dopamine levels are the lowest and decrease in morning hours when dopamine levels are higher, in compliance with dopamine circadian rhythm. Dopaminergic agents are used for primary RLS treatment; however etiology-focused treatments are preferred for secondary RLS (pregnancy, end stage renal failure and anemia) [13].

Parkinson's disease is characterized by the loss of dopaminergic cells gradually in the nigrostriatal pathway. Early findings of Parkinson's disease were observed in case of bradykinesia, walking disorders, rigidity, and the loss of tremor strial dopamine at a rate of 80-90% and nigral dopaminergic neurons at a rate of 50% [14-17]. In a cohort study conducted by Knekt et al., in Finland, they examined the relationship between vitamin D levels and risk of Parkinson's disease and as a result of 29-year follow-up of 3713 individuals above the age of 50, they found out that the individuals, who had low vitamin D levels, in the beginning, had higher risk of Parkinson's disease [18]. In a study conducted by Evatt et al., with Parkinson's and Alzheimer's disease patients, they found out that the vitamin D deficiency prevalence of Parkinson's disease patients was higher compared to Alzheimer's and control groups. Researchers reported that the vitamin D insufficiency in Parkinson's disease patients was 55% whereas vitamin D deficiency was 23% [19].

In a recently conducted study, the presence of vitamin D receptor was proved in the dopaminergic neurons in human and rat brains. Due to the nuclear location of vitamin D receptors, it is asserted that vitamin D could affect cell proliferation, differentiation and even life cycles in these neurons. These results support the relationship of abnormal dopaminergic transmission diseases such as schizophrenia and Parkinson's disease with vitamin D [20].

It was reported in an in-vitro study that the increasing intense expression of vitamin D receptors in dopamine neurons in the brain, especially in the substantia nigra area increased the expression of tyrosine hydroxylase which is a rate-limiting enzyme in dopamine synthesis in adrenal medulla cells with the effect of 1.25 (OH) D2, D3 [21]. In addition, both vitamin D receptors and 1 alpha-hydroxylase enzyme are expressed in human brain, especially in substantia nigra neurons (probably dopaminergic) [22]. In animal experiments, it has been showed that 1.25 dihydroxy vitamin D which is the active metabolite of vitamin D could partly protect neurons against ischemic brain damage and the damages caused by 6- hydroxydopamine (a substance used to create Parkinson) [23-24].

In a study conducted by Balaban et al., 25 (OH) vitamin D levels of 36 patients with RLS (28 women and 8 men) were compared with 25 (OH) vitamin D levels of 38 healthy patients (27 female and 11 men). In this study, patients with secondary reason related RLS were not included in the study. While vitamin D level was 7.31 ng/mL in female patients with RLS, it was 12.31 mg/mL in healthy females. When two groups were compared, 25 (OH) vitamin D levels were significantly low in the group of patients with RLS (p=0.001) [25]. In this study, 25 (OH) vitamin D levels of 33 individuals with RLS were 10.76 ±4.56 whereas the 25 (OH) vitamin D levels of 42 individuals without RLS were 14.18±7.02. A significant relation was determined between the 25 (OH) vitamin D levels and RLS. (p=0.018).

Iron deficiency is related to RLS. It plays an important role in secondary reasons such as pregnancy and anemia. Iron is required as a cofactor for tyrosine hydroxylase, which is the rate-limiting enzyme for the formation of dopamine from levodopa. Therefore, dopamine synthesis may decrease in case of iron

deficiency. A significant improvement is observed in some cases of RLS through iron treatment. In addition, iron concentration is also found to be low in substantia nigra in RLS patients [26-27]. In all groups where iron deficiency incidence is high, and in cases of pregnancy, end-stage renal failure and anemia, RLS incidence was 20-30% [27]. However, 75% of individuals with RLS are known to have decreasing iron stores [28]. In a study conducted on 79 patients with iron deficiency, 58% of patients had 25 (OH) vitamin D levels of < 30 ng/ml whereas 39% had levels of < 20 ng/ml [29]. In a study conducted by Balaban et al., ferritin levels between the groups with and without RLS were also found different, and ferritin levels were found lower in the women patients with RLS [25]. In a study conducted by Zbroch et al., dialysis (75 hemodialyses and 26 peritoneal dialyzes) patients were included in the study and dopamine levels of patients were low [30]. In this study, no significant relation was determined between anemia and RLS.

Consequently, vitamin D levels were significantly lower in hemodialysis patients with RLS. 25 (OH) vitamin D may be a factor for RLS etiology in hemodialysis patients. The fact that 25 (OH) vitamin D deficiency is frequent in CKD and dopamine level is low is an indicator that vitamin D deficiency may be responsible for dopamine deficiency in CKD.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding

None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Hüzmeli C, Candan F, Timucin M, Alaygut D, Akkaya L, Şeker A, Kayataş M. The relationship between restless leg syndrome and 25-hydroxy D vitamin in hemodialysis patients. J Clin Anal Med 2018;9(1): 65-8.